SUMMARY OF PRODUCT CHARACTERISTICS
Republic of Ireland Specific
**1. Name of the medicinal product**

LG-octaplas solution for infusion.

**2. Qualitative and quantitative composition**

LG-octaplas is presented as a solution for infusion containing 45 - 70 mg human plasma proteins/mL. For details about important coagulation factors and inhibitors, see section 5.1 and table 2. For a full list of excipients, see section 6.1.

**3. Pharmaceutical form**

LG-octaplas is supplied as a frozen solution, which appears (slightly) yellow.

**4. Clinical particulars**

**4.1 Therapeutic indications**

- Complex deficiencies of coagulation factors such as coagulopathy due to severe hepatic failure or massive transfusion.
- Substitution therapy in coagulation factor deficiencies, when a specific coagulation factor concentrate (e.g. factor V or factor XI) is not available for use or in emergency situations when a precise laboratory diagnosis is not possible.
- Rapid reversal of the effects of oral anticoagulants (coumarin or indanedione type), when a prothrombin complex concentrate is not available for use or administration of vitamin K is insufficient due to impaired liver function or in emergency situations.
- Potentially dangerous haemorrhages during fibrinolytic therapy, using e.g. tissue plasminogen activators, in patients who fail to respond to conventional measures.
- Therapeutic plasma exchange procedures, including those in thrombotic thrombocytopenic purpura (TTP).

**4.2 Posology and method of administration**

**Dosage:**

The dosage depends upon the clinical situation and underlying disorder, but 12 - 15 mL LG-octaplas/kg body weight is a generally accepted starting dose. This should increase the patient's plasma coagulation factor levels by approximately 25%.

It is important to monitor the response, both clinically and with measurement of e.g. activated partial thromboplastin time (aPTT), prothrombin time (PT), and/or specific coagulation factor assays.
Dosage for coagulation factor deficiencies:

An adequate haemostatic effect in minor and moderate haemorrhages or surgery in coagulation factor deficient patients is normally achieved after the infusion of 5 - 20 mL LG-octaplas/kg body weight. This should increase the patient's plasma coagulation factor levels by approximately 10 - 33%. In the event of major haemorrhage or surgery, the expert advice of a haematologist should be sought.

Dosage for TTP and haemorrhages in intensive plasma exchange:

For therapeutic plasma exchange procedures, the expert advice of a haematologist should be sought.

In TTP patients the whole plasma volume exchanged should be replaced with LG-octaplas.

Method of administration:

Administration of LG-octaplas must be based on ABO-blood group compatibility. In emergency cases, LG-octaplas blood group AB can be regarded as universal plasma since it can be given to all patients regardless of blood group.

LG-octaplas must be administered by intravenous infusion after thawing, as described in section 6.6, using an infusion set with a filter. An aseptic technique must be used throughout the infusion.

Due to the risk of citrate toxicity, the infusion rate should not exceed 0.020 - 0.025 mmol citrate/kg body mass/minute - equal to ≤1 mL LG-octaplas/kg body mass/minute. Toxic effects of citrate can be minimised by giving calcium gluconate intravenously into another vein.

Use in children:
The experience in children is limited.

4.3 Contraindications

- IgA deficiency with documented antibodies against IgA.
- Hypersensitivity to the active substance, any of the excipients or residues from the manufacturing process, as stated in section 5.3.
- Severe deficiencies of protein S.

4.4 Special warnings and precautions for use

LG-octaplas should not be used:

- As volume expander.
- In cases of bleeding caused by coagulation factor deficiencies where a specific factor concentrate is available for use.
• To correct hyperfibrinolysis in liver transplantation or other conditions with complex disturbances of haemostasis caused by a deficiency of plasmin inhibitor, also named α2-antiplasmin.

**LG-octaplas should be used with caution under the following conditions:**

• IgA deficiency.
• Plasma protein allergy.
• Previous reactions to fresh-frozen plasma (FFP) or LG-octaplas.
• Manifest or latent cardiac decompensation.
• Pulmonary oedema.

In order to reduce the risk for venous thromboembolism caused by the reduced protein S activity of LG-octaplas compared to normal plasma (see section 5.1), caution should be exercised and appropriate measures should be considered in all patients at risk for thrombotic complications.

In intensive plasma exchange procedures, LG-octaplas should only be used to correct the coagulation abnormality when abnormal haemorrhage occurs.

Standard measures to prevent infections resulting from the use of medical products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pool for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses and prions. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown and emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV.

The measures taken may be of limited value against non-enveloped virus such as HAV, HEV and Parvovirus B19. Parvovirus B19 infection may be serious for pregnant woman (fetal infection) and for individuals with immuno-deficiency or increased erythropoiesis (e.g. haemolytic anaemia). HEV may also seriously affect seronegative pregnant women. Therefore LG-octaplas should only be administered to these patients if strongly indicated.

Appropriate vaccination (e.g. against HBV and HAV) for patients in regular receipt of medicinal products derived from human blood or plasma should be considered.
It is strongly recommended that every time that LG-octaplas is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Administration of LG-octaplas must be based on ABO-blood group compatibility. In emergency cases, LG-octaplas blood group AB can be regarded as universal plasma since it can be given to all patients regardless of blood group.

Patients should be observed for at least 20 minutes after the administration.

In case of anaphylactic reaction or shock, the infusion must be stopped immediately. Treatment should follow the guidelines for shock therapy.

Data on the use of LG-octaplas in premature babies are very limited, therefore, the product should only be administered to these individuals if the likely benefits clearly outweigh potential risks.

**4.5 Interaction with other medicinal products and other forms of interactions**

**Interactions:**

No interactions with other drugs have been identified.

**Incompatibilities:**

- LG-octaplas product can be mixed with red blood cells and platelets.
- LG-octaplas must not be mixed with other drugs, as inactivation and precipitation may occur.
- To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as LG-octaplas.

**4.6 Fertility, pregnancy and lactation**

The safety of LG-octaplas for use in human pregnancy has not been established in controlled clinical trials. The product should be administered to a pregnant or lactating woman only if alternative therapies are regarded inappropriate.

For potential risk of Parvovirus B19 and HEV transmission, see section 4.4.

**4.7 Effects on ability to drive and use machines**

After ambulant infusion, the patient should rest for one hour.

There are no indications that LG-octaplas may impair the ability to drive or to operate machines.
4.8 Undesirable effects

- Acute mild allergic reaction due to hypersensitivity to infused proteins and characterised by urticaria, fever, chills, nausea, vomiting, and abdominal or back pain may commonly be observed.

- Acute and sometimes severe allergic (anaphylactic or anaphylactoid) type of reactions characterised by flushing, hypotension, chest pain, bronchospasms, dyspnoea, and cardio-respiratory collapse may rarely be observed.

- High infusion rates may rarely cause cardiovascular effects as a result of citrate toxicity (fall in ionised calcium), especially in patients with liver function disorders. In the course of plasma exchange procedures, symptoms attributable to citrate toxicity such as fatigue, paraesthesia, tremor, and hypocalcemia may be observed rarely.

- Administration of LG-octaplas must be based on ABO-blood group compatibility. In case of an incompatible transfusion by mistake, ABO-antibodies in LG-octaplas will bind to the antigens of recipient red blood cells and cause an immediate or delayed type of haemolytic transfusion reactions.

- For safety with respect to transmissible agents, see section 4.4

During clinical trials with LG-octaplas’s predecessor product, and its post-approval use, the following adverse reactions have been identified:
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common (≥1% to ≤10%)</th>
<th>Uncommon (≥0.1% to ≤1%)</th>
<th>Rare (≥0.01% to &lt;0.1%)</th>
<th>Very Rare (&lt;0.01%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
<td>haemolytic anaemia</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>anaphylactic reaction</td>
<td>anaphylactic shock</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>anaphylactoid reaction</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>hypersensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>citrate toxicity</td>
<td></td>
<td>alkalosis</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td>agitation</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>hypotension</td>
<td>flushing haemorrhagic diathesis</td>
<td>arrhythmia cardiac arrest</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td>bronchospasm respiratory disorder</td>
<td>flushing haemorrhagic diathesis</td>
<td>thromboembolism hypertension circulatory collapse</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>dyspnoea</td>
<td>acute pulmonary oedema pulmonary haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>nausea</td>
<td>vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rash pruritus</td>
<td>urticaria</td>
<td>rash erythematous hyperhidrosis</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>chills pyrexia</td>
<td>localised oedema</td>
<td>chest pain</td>
<td>application site reaction</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td>antibody test positive</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
<td>haemolytic transfusion reaction</td>
<td></td>
</tr>
</tbody>
</table>
4.9 Overdose

- High dosages or infusion rates may induce hypervolaemia, pulmonary oedema and/or cardiac failure.

- High infusion rates may cause cardiovascular effects as a result of citrate toxicity (fall in ionised calcium), especially in patients with liver function disorders.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plasma substitutes and plasma protein fractions, ATC code: B05A A.

The content and distribution of plasma proteins in LG-octaplas remain in the final product at comparable levels to those in the raw material FFP, i.e. 45 - 70 mg/mL, and the major plasma proteins are all within the reference ranges for healthy blood donors (see table 2). Out of a mean total protein content of 58 mg/mL, albumin accounts for 50% (29 mg/mL), whereas the immunoglobulin classes G, A, and M are present at levels of 8.1, 1.6, and 0.8 mg/mL, respectively. As a result of the S/D treatment and purification, the content in lipids and lipoproteins is reduced. This is of no relevance within the indications for LG-octaplas.

The manufacturing process levels out inter-donor variations and maintain the plasma proteins in a functional state. Therefore, LG-octaplas possesses the same clinical activity as the average single-donor FFP unit, but is more standardised. The finished product is tested for coagulation factors V, VIII, and XI, and the inhibitors protein C, protein S, and plasmin inhibitor. A minimum of 0.5 IU/mL is obtained for each of the three coagulation factors, whereas the inhibitor levels are guaranteed equal or higher than 0.7, 0.3, and 0.2 IU/mL. The fibrinogen content is between 1.5 and 4.0 mg/mL. In routine production, all clinically important parameters are within the 2.5 - 97.5 percentiles reference range for single-donor FFP, except plasmin inhibitor (also known as α2-antiplasmin) that is just below (see table 2). LG-octaplas displays the same von Willebrand factor multimeric pattern as normal plasma.
Table 2: Global coagulation parameters and specific coagulation factors and inhibitors in LG-octaplas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LG-octaplas Mean ± standard deviation (n = 5)</th>
<th>Reference range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated partial thromboplastin time [sec]</td>
<td>30 ± 1</td>
<td>28-41</td>
</tr>
<tr>
<td>Prothrombin time [sec]</td>
<td>11 ± 0</td>
<td>10-14**</td>
</tr>
<tr>
<td>Fibrinogen [mg/mL]</td>
<td>2.6 ± 0.1</td>
<td>1.5-4.0**</td>
</tr>
<tr>
<td>Coagulation factor II [IU/mL]</td>
<td>1.01 ± 0.07</td>
<td>0.65-1.54</td>
</tr>
<tr>
<td>Coagulation factor V [IU/mL]</td>
<td>0.76 ± 0.05</td>
<td>0.54-1.45</td>
</tr>
<tr>
<td>Coagulation factor VII [IU/mL]</td>
<td>1.09 ± 0.05</td>
<td>0.62-1.65</td>
</tr>
<tr>
<td>Coagulation factor VIII [IU/mL]</td>
<td>0.80 ± 0.07</td>
<td>0.45-1.68</td>
</tr>
<tr>
<td>Coagulation factor IX [IU/mL]</td>
<td>0.88 ± 0.10</td>
<td>0.45-1.48</td>
</tr>
<tr>
<td>Coagulation factor X [IU/mL]</td>
<td>0.99 ± 0.05</td>
<td>0.68-1.48</td>
</tr>
<tr>
<td>Coagulation factor XI [IU/mL]</td>
<td>0.88 ± 0.04</td>
<td>0.42-1.44</td>
</tr>
<tr>
<td>Coagulation factor XII [IU/mL]</td>
<td>1.04 ± 0.08</td>
<td>0.40-1.52</td>
</tr>
<tr>
<td>Coagulation factor XIII [IU/mL]</td>
<td>1.03 ± 0.06</td>
<td>0.65-1.65</td>
</tr>
<tr>
<td>Antithrombin [IU/mL]</td>
<td>0.86 ± 0.11</td>
<td>0.72-1.45</td>
</tr>
<tr>
<td>Heparin cofactor II [IU/mL]</td>
<td>1.12 ± 0.05</td>
<td>0.65-1.35</td>
</tr>
<tr>
<td>Protein C [IU/mL]</td>
<td>0.86 ± 0.08</td>
<td>0.58-1.64</td>
</tr>
<tr>
<td>Protein S [IU/mL]</td>
<td>0.63 ± 0.08</td>
<td>0.56-1.68</td>
</tr>
<tr>
<td>Von Willebrand factor ristocetin cofactor activity [IU/mL]</td>
<td>0.93 ± 0.08</td>
<td>0.45-1.75</td>
</tr>
<tr>
<td>ADAMTS13* activity [IU/mL]</td>
<td>1.13 ± 0.17</td>
<td>0.50-1.10**</td>
</tr>
<tr>
<td>Plasminogen [IU/mL]</td>
<td>0.84 ± 0.06</td>
<td>0.68-1.44</td>
</tr>
<tr>
<td>Plasmin inhibitor## [IU/mL]</td>
<td>0.61 ± 0.04</td>
<td>0.72-1.32</td>
</tr>
</tbody>
</table>

* According1,2 based on the testing of 100 healthy blood donors and defined by the 2.5 and 97.5 percentiles; or **according package insert of test kit.

## A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13. Also known as von Willebrand factor-cleaving protease (VWFCP).

## Also known as α2-antiplasmin.

5.2 Pharmacokinetic properties

LG-octaplas has similar pharmacokinetic properties as FFP.

5.3 Preclinical safety data

Virus inactivation is carried out using Tri (N-Butyl) Phosphate (TNBP) and Octoxynol (Triton X-100). These S/D reagents are removed during the purification process. The maximum amounts of TNBP and Octoxynol in the finished product are 2 µg/mL and 5 µg/mL, respectively.

Pharmacological and toxicological studies in animals indicate that these residual levels should present no clinical problem for the indications and dosages specified.

6. Pharmaceutical Particulars

6.1 List of excipients
- Sodium citrate dihydrate
- Sodium dihydrogenphosphate dihydrate
- Glycine

6.2 Incompatibilities
- LG-octaplas product can be mixed with red blood cells and platelets.
- LG-octaplas must not be mixed with other drugs, as inactivation and precipitation may occur.
- To avoid the possibility of clot formation, solutions containing calcium must not be administered by the same intravenous line as LG-octaplas.

6.3 Shelf-life
The shelf-life of LG-octaplas is 4 years when stored at ≤ -18°C and protected from light.

After thawing LG-octaplas can be stored for up to 24 hours at +2 - 8°C, or 8 hours at room temperature (+20 - 25°C), before use.

Once the bag has been opened, the product must be used immediately.

6.4 Special precautions for storage
The frozen LG-octaplas product should be stored and transported according to the temperature and conditions as mentioned above (see section 6.3).

6.5 Nature and contents of container
LG-octaplas is filled into sterile, plasticised polyvinyl chloride blood bags that are over-wrapped with a polyamide/polyethylene film.

One bag contains 200 mL of LG-octaplas.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
LG-octaplas should be transported and stored at ≤ -18°C.

Do not use after the expiry date given on the label.

There are several options for thawing frozen LG-octaplas:
- Water bath:
  Thaw in the outer wrapper in a water bath with good circulation at +30 to +37°C. It is important to prevent water from contaminating the entry port. Temperature in the water bath must never exceed +37°C and should not be lower than +30°C. The thawing procedure should not take more than 30 minutes.
• Using a dry tempering system such as the SAHARA-III: Place the LG-octaplas bags on the agitation plate according to the manufacturer instructions and thaw plasma using the fast tempering function. When a +37°C blood component temperature is indicated on the temperature display, terminate the tempering process and remove the bags. During thawing of LG-octaplas using a dry tempering system, it is recommended to use the protocol printer to record the course of the blood component temperature and error messages in event of failure.

• Others: Other thawing systems for frozen LG-octaplas can be used on the condition that the methods are validated for that purpose.

Allow the content of the bag to warm to approximately +37°C before infusion. The temperature of LG-octaplas must not exceed +37°C. Remove the outer wrapper and examine the bag for cracks or leaks.

Avoid shaking.

Do not use solutions which are cloudy or have deposits.

Thawed LG-octaplas must not be refrozen. Unused product must be discarded.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
   Octapharma Limited
   The Zenith Building
   26 Spring Gardens
   Manchester
   M2 1AB

8. Marketing authorisation number
   PA 521/4/2

9. Date of first authorisation/renewal of the authorisation
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   Date of last renewal: 4th March 2008

10. Date of revision of the text
    January 2014